



ADME Hub: Desktop Software for Linking Metabolic Profiling Assays and LC/MS/MS Bioanalysis in Drug Discovery

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Introduction

New chemical entities (NCE) cycle through the ADME-screening group on a weekly basis. There is often extensive follow-up of molecules as subsequent work measures a broader range of in vitro metabolic properties. The ADME-workflow occurs throughout the drug discovery lifecycle until a NCE is nominated into drug development or abandoned. We describe here the use of a desktop software module that seamlessly ties together the ADME workflow from assay design through LC/MS/MS bioanalysis. This approach reduces data turnaround time by allowing the analyst a means of linking (and automating) the ADME profiling experiment and LC/MS/MS bioanalysis.

ADME Hub Workflow

Figure 1. ADME Hub Workflow

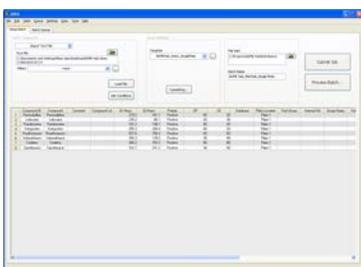
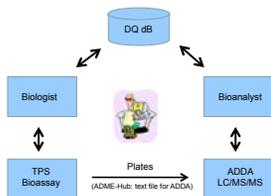


Figure 2. ADME Hub Setup Tab: Biologist imports list of compounds (see Figure 2) to be assayed. Compounds are checked against ADME-Hub database.



Figure 5. Apricot Designs TPS Robot



Figure 6. Preparation Instructions

Biologist can either manually run the assay or generate a file to import into the Apricot TPS Robot (see Figure 5). A PDF output file can be generated that lists the assay protocol for use at the laboratory bench top (see Figure 6). The file can also be stored and serves as a time stamp record of the experiment.

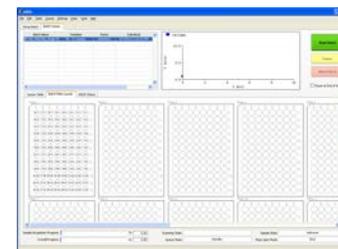


Figure 9. ADDA Batch Queue Panel, Single Plate : Bioanalytical scientist has loaded the plates and starts the batch

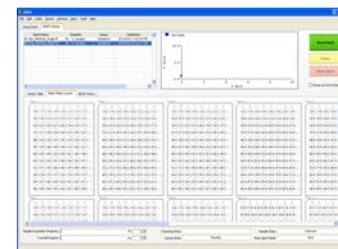


Figure 10. ADDA Batch Queue Panel Multiple Plates: : Bioanalytical scientist has loaded the plates and starts the batch

Objectives

Develop software to expedite high-throughput analysis of non-standard experimental formats in drug discovery.

Provide interface for "open-access" use of biology automation

Methods

DiscoveryQuant-Optimize was used to acquire MS/MS conditions for NCEs, conditions were stored in a central database (the ADME-Hub).

A software module was developed that facilitated experimental setup for manual and/or automated (TPS robot) ADME studies.

ADME assay templates were stored along with MS/MS conditions in the ADME-Hub database.

The ADME-Hub assigns plate, well and sample information to a given experiment (plates can be assigned barcode identifiers).

The experimental protocol is downloaded at the TPS robot to run the given ADME study.

When the assay is complete sample plates were transferred to the ADDA. The injection sequence and compound information is retrieved by barcode at the LC/MS/MS workstation prior to bioanalysis.

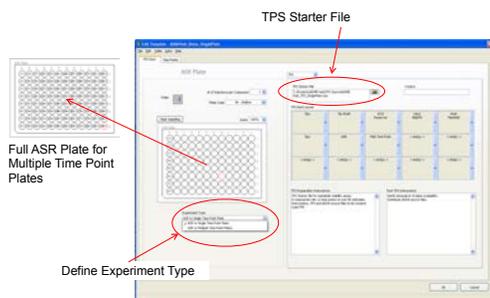


Figure 3. ADME Hub Template TPS Deck.: An Assay Design Template is created. Assay Ready Plate (ASR) is defined by designating well locations for the imported compounds. TPS Deck information is obtained from a TPS starter method.

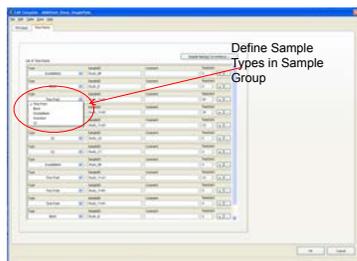


Figure 4. ADME Hub Template Time Points :user can identify sample type for each compound, BLK and control plates can be added separately .

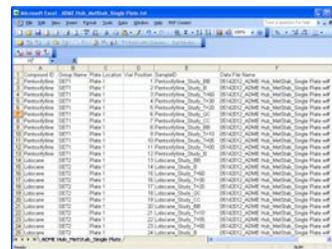


Figure 7. ADDA Source File: An ADDA source file (see Figure 7) is created and stored on a central server and is available for download in the ADDA Software.

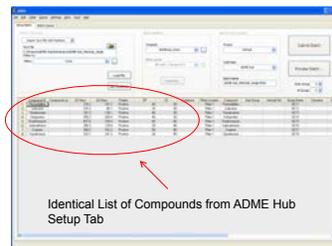


Figure 8. ADDA Setup Panel: Bioanalyst downloads batch from ADME-Hub experiment file, and loads sample plates onto ADDA to start LC/MS/MS analysis.

Summary and Conclusions:

As ADME studies expand and each study becomes unique and less standardized, significant time can be lost in communicating study design and compounds tested through to bioanalytical personnel.

he ADME-Hub software was designed to adapt the ADME-screening workflow to non-standardized in vitro assays.

The ADME-Hub uses the DQ-database of compounds and MS/MS conditions to guide the experimenter through assay setup, making certain compounds are available in the database, and plate formats, and sampling sequence are optimized for the autosampler and analytical method.

The ADME-Hub run file is then placed in a central server to be downloaded at the plate layout and contents; this allows the analyst to focus on analytical quality and return of endpoint data. This approach is illustrated for metabolic stability studies of varying experimental design.

This approach significantly simplifies or removes the communication step relative to the plate layout and contents; this allows the analyst to focus on analytical quality and return of endpoint data. This approach is illustrated for metabolic stability studies of varying experimental design.